The metabolic response to trauma

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Abstract

Trauma is a term used to encompass a wide range of pathologies. It results in a complex response initially described in 1942 as an acute 'ebb' phase of catabolism followed by anabolism in the 'flow phase'. Others have described the process as a 'nervous' initial phase, closely followed by an 'immune' phase which then develops into a late 'endocrine' phase. Initially there is a shift to anaerobic glycolysis in the resulting hypoxic environment. Hypotension and tachycardia occur alongside increased vessel permeability and vasodilatation. Lipolysis and glycogenolysis have key roles in substrate supply, with insulin resistance and increased gluconeogenesis resulting in ongoing hyperglycaemia but with relatively poor utilization. Proteolysis of skeletal muscle to supply energy substrates can result in limitations in wound healing and rehabilitation. Acutely, acidosis and hypothermia are implicated in trauma-induced coagulopathy, with tissue hypoperfusion an additional risk factor. Hypercoagulability may also be seen, due to impaired anticoagulant activity, particularly in penetrating trauma. Neutrophils and macrophages are attracted to injured sites as part of the immune response, alongside both a cytokine and acute phase protein response. Clinicians should understand these processes and implicate measures to limit the potential adverse effects of the body's metabolic response.

Keywords Catabolism; cytokines; ebb; flow; glycolysis; immune response; metabolic; trauma

The term trauma is used to encompass a wide range of pathologies, including injury secondary to violence or accident, and affects patients throughout the ages, with a growing presentation in the elderly.[1] Traditionally severe trauma is recognized as those with an Injury Severity Score (ISS) >15.[1] Due to the large range in pathologies encompassed, the metabolic response is complex; in 1942 Cuthbertson et al. (Figure 1) outlined this complexity describing an acute 24–48 hours 'ebb' period of catabolism and 'flow' period as the body moves from catabolism to anabolism over the next two to three weeks.[2] This theory has been further developed in the 21st century into an immediate 'nervous' phase with resulting cellular oedema, ischaemia secondary to vasoconstriction and then vasodilatation with reperfusion; an intermediate 'immune' phase with platelet aggregation, hypermetabolism and bacterial translocation; and a late 'endocrine' phase with catabolism moving to anabolism and angiogenesis.[3] This article aims to outline some of the current key principles behind this response in an A to E structure.

Airway and breathing

Trauma initiates a period of stress within the body, resulting in an increased oxygen requirement and hence increased respiratory rate. Indeed, an increased respiratory rate is often recognized as a key observation in a deteriorating patient but may also be a sign of pain or psychological distress. However, within the tissues affected by injury, in the immediate phase a hypoxic environment develops resulting in the anaerobic glycolysis, lactate production, cellular acidosis and oxidative stress.[3] Hypoxia inducible factor-1 is thought to be one of the key hypoxia responsive genes involved in initiating this process.[3] Injured cells undergo glycolysis rather than oxidative phosphorylation, a less efficient method in producing adenosine triphosphate (ATP).[3] The reactive oxygen and nitrogen species generated are also though to contribute to the breakdown of proteins and lipids.[3] This underlying process, in addition to the cellular oedema, interstitial oedema and later systemic inflammatory response seen in the immediate and intermediate phase and the

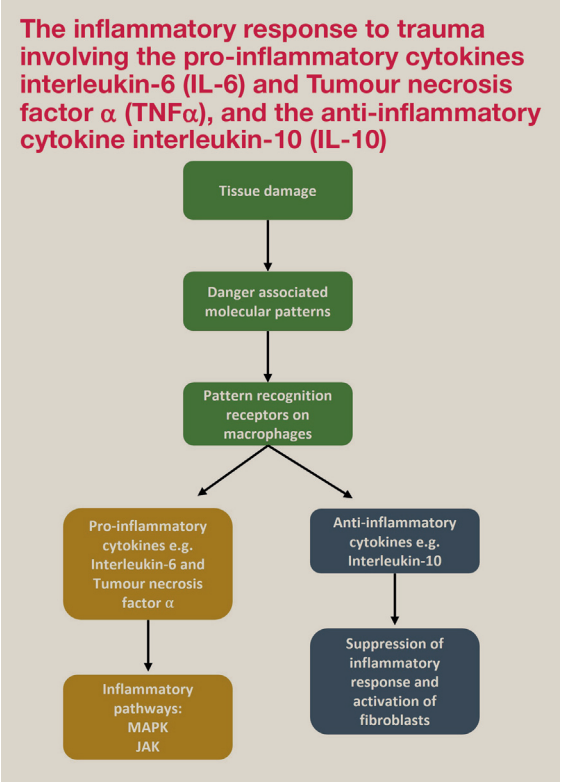
The inflammatory response to trauma involving the pro-inflammatory cytokines interleukin-6 (IL-6) and Tumour necrosis factor α (TNFα), and the anti-inflammatory cytokine interleukin-10 (IL-10)
Tissue damage
Danger associated molecular patterns
Pattern recognition receptors on macrophages
Pro-inflammatory cytokines e.g. Interleukin-6 and Tumour necrosis factor α
Anti-inflammatory cytokines e.g. Interleukin-10
Inflammatory pathways: MAPK JAK
Suppression of inflammatory response and activation of fibroblasts

Figure 1

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underlying injuries often obtained through trauma (for example pulmonary contusions) are thought to contribute to the clinical development of acute respiratory distress syndrome (ARDS), commonly seen in trauma patients.[4] Additionally, from the immune phase onwards, the development of a systemic inflammatory response syndrome (SIRS)-like response often results in ongoing tachypnoea.[3]

Circulation

Initially within the circulatory system hypotension and tachycardia can be observed, normally as a direct result of haemorrhage resulting in hypovolaemia. However, other causes of shock such as neurogenic shock and obstructive shock should not be forgotten.[5]

At a vessel level, within the first 10–15 minutes vasoconstriction is seen.[3] However, this quickly transitions to vasodilatation due to the production of various proteins such as leukotrienes, prostaglandins and histamine.[3] Oedema and increased vascular permeability also occurs secondary to histamine, bradykinin and substance P being produced.[3] It is thought this vasodilatation was initially to allow cells to receive energy substates via diffusion.[3] Additionally, the hypothalamic–pituitary–adrenal (HPA) axis and adrenomedullary system is activated with increased production of adrenaline and glucocorticoids.[3] This is thought to be a protective measure by the body to contain the inflammatory response at the site of injury.[3] There is also likely to be diversion of the blood flow away from certain vasculature, for example splanchnic blood flow has been shown to decrease with hypovolaemia.[6] It is thought this blood flow diversion is likely to contribute to the barrier dysfunction seen particularly in the gut, resulting in bacterial translocation.[6] However, as the body progresses into the immune phase, the more systemic response occurs, resulting in the tachycardia and hypotension associated with SIRS.[3] Additionally, trauma patients are at risk of developing infection and sepsis, again resulting in tachycardia and hypotension.[3]

It is likely that there is a difference between the presentation of blunt and penetrating trauma. Penetrating trauma can result in less cellular injury but will still result in hypovolaemia and metabolic changes.[7] As a result there will be activation of the renin–angiotensin–aldosterone system (RAAS) with increased production of renin and as a result angiotensin II, again resulting in vasoconstriction.[7] Additionally there will be increased antidiuretic hormone (ADH; vasopressin) production by the hypothalamus resulting in increased vasoconstriction and water reabsorption at the collecting ducts in the kidneys.[7] This vasoconstriction can result in significant ischaemia to originally non-injured organs. If wider-spread injury, i.e. in blunt trauma, these mechanisms and metabolic changes will still occur but with more of an inflammatory response and more of a diversion of blood flow away from metabolically active organs.[8]

Don't ever forget glucose

The energy source for metabolism during trauma is hugely important. The initial nervous and immune phases both result in increased anaerobic glycolysis, as described above.[3] Following this a phase of catabolism develops, often known as a hypermetabolic state.[3,9] The following anabolic phase may take more than three weeks to develop, as has been shown in burns patients, during which large amounts of body protein are lost.[10,11]

It is thought that the increased catecholamines seen during the acute phase of the injury results in hormones such as adrenaline, cortisol and glucagon increasing within the bloodstream, all of which encourage catabolism.[9,10] Additionally, the rise in cytokines, such as TNF-α and interleukin (IL)-6 may also encourage protein breakdown.[10] Insulin will start to rise but slightly later in the acute phase.[10] Immediately following the injury there is a relative inhibition of insulin secretion and as a result a rise in blood glucose and fatty acid levels.[10] However, despite the hyperglycaemia, utilization by cells for metabolism is poor due to patients also developing a relative insulin resistance.[10] There will therefore be increased gluconeogenesis and protein breakdown to ensure sufficient metabolic substrates for energy production. Hyperglycaemia is therefore a common complication of severe trauma and many patients will require insulin infusions as we target normoglycaemia.

Amino acids are not only utilized for gluconeogenesis but also diverted into the production of acute phase proteins such as C reactive protein (CRP). However, this diversion to facilitate this production will result in overall muscle protein loss.[10] It is thought the more severe the injury the greater the rate of protein breakdown.[10] The consequences of this catabolism are huge for the patient, including impaired wound healing, hypoalbuminaemia, muscle wasting (and therefore limitations in rehabilitation) and impaired ability to fight infection.[11]

The hypermetabolic state post severe trauma therefore requires adequate calorie replacement; it is estimated that in severely injured patients their energy expenditure increases by 30%–40% and in severe burns patients as much as 70%.[10] Enteral feeding started within 24 hours has been shown to be most effective when tested in burns patients, with predominantly carbohydrate-based calories having the greatest impact.[9] The benefits are likely to be huge to our patients and it is important we consider the underlying mechanisms that have precipitated this.

Electrolytes and fluid

The original 1942 work showed that during days four to eight there is an increase in urinary nitrogen excretion, presumed to be from skeletal protein muscle breakdown.[2] The activation of the RAAS (Figure 2) and HPA axis can also result in electrolyte abnormalities. Regarding fluids, the fluid shifts seen during the initial immune phase have been described above. Alongside the hypovolaemia, relative poor perfusion of the kidneys and additional risk factors, such as creatine kinase release from damaged muscles, trauma patients are at risk of both acute kidney injury (AKI) and fluid overload. Additionally, iatrogenic injury can occur in the attempted resuscitation of trauma patients. Clinically, outside of the initial resuscitation, a more fluid restrictive management plan for these patients is likely to be beneficial for various outcome measures.[12]

Haematology

Coagulation and clotting are critical in trauma (Figure 3). It is thought that at least one quarter of major trauma patients may experience a coagulopathy, which increases their mortality by up to four times.[13] The combination of acidosis, hypocalcaemia and

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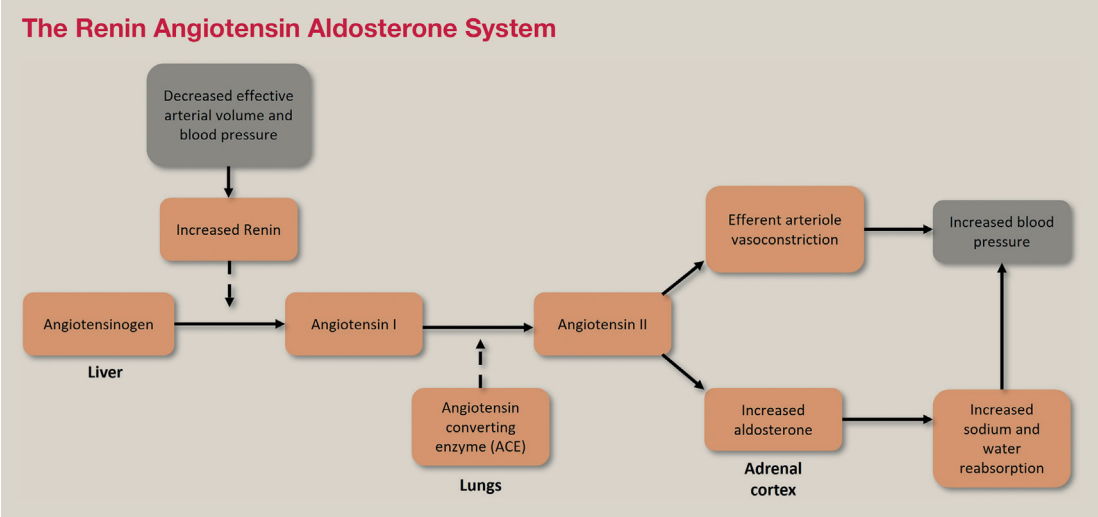

Figure 2

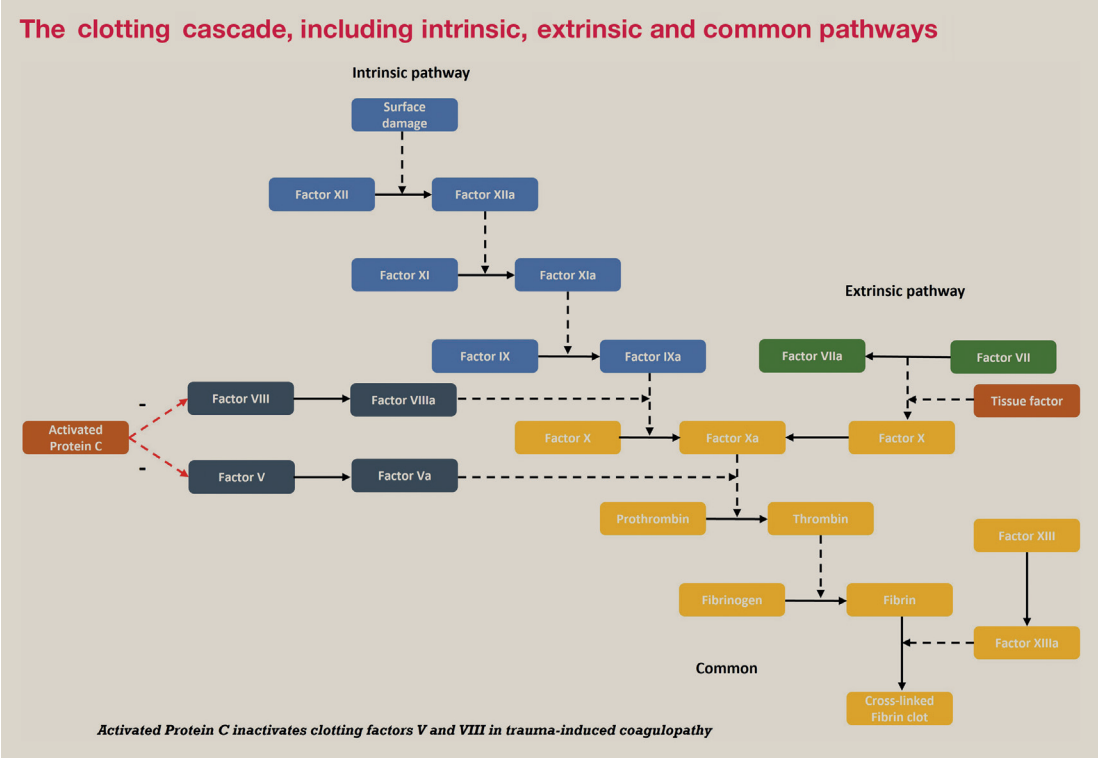

Figure 3

hypothermia all contribute to the development of trauma-induced coagulopathy.

Following severe injury, the sympathoadrenal activation leads to endothelial activation.[14] The proinflammatory mediators activate the coagulation system. Clots must form, and also be dissolved, to allow blood flow and tissue perfusion to continue.[14] Brohi et al. have shown that the body will continue to produce sufficient prothrombin and fibrinogen in the acute phase of trauma to facilitate clot formation.[13] Indeed, the acute trauma-induced coagulopathy only appears to occur when there is tissue hypoperfusion, resulting in increased activation of the anticoagulant Protein C (leading to inhibition of clotting factors V and VIII).[13] As a result, the suggestion to clinicians is to prevent the tissue hypoperfusion from occurring.[13]

Hypercoagulability can also occur following trauma. Normally thrombin generated at the site of the tissue injury is modulated by anti-coagulants, such as protein C, preventing the development of thrombosis.[14] However, if in a pro-coagulant state and there is impairment of the anticoagulant activity, there is an increased risk of thrombosis developing.[14] There is

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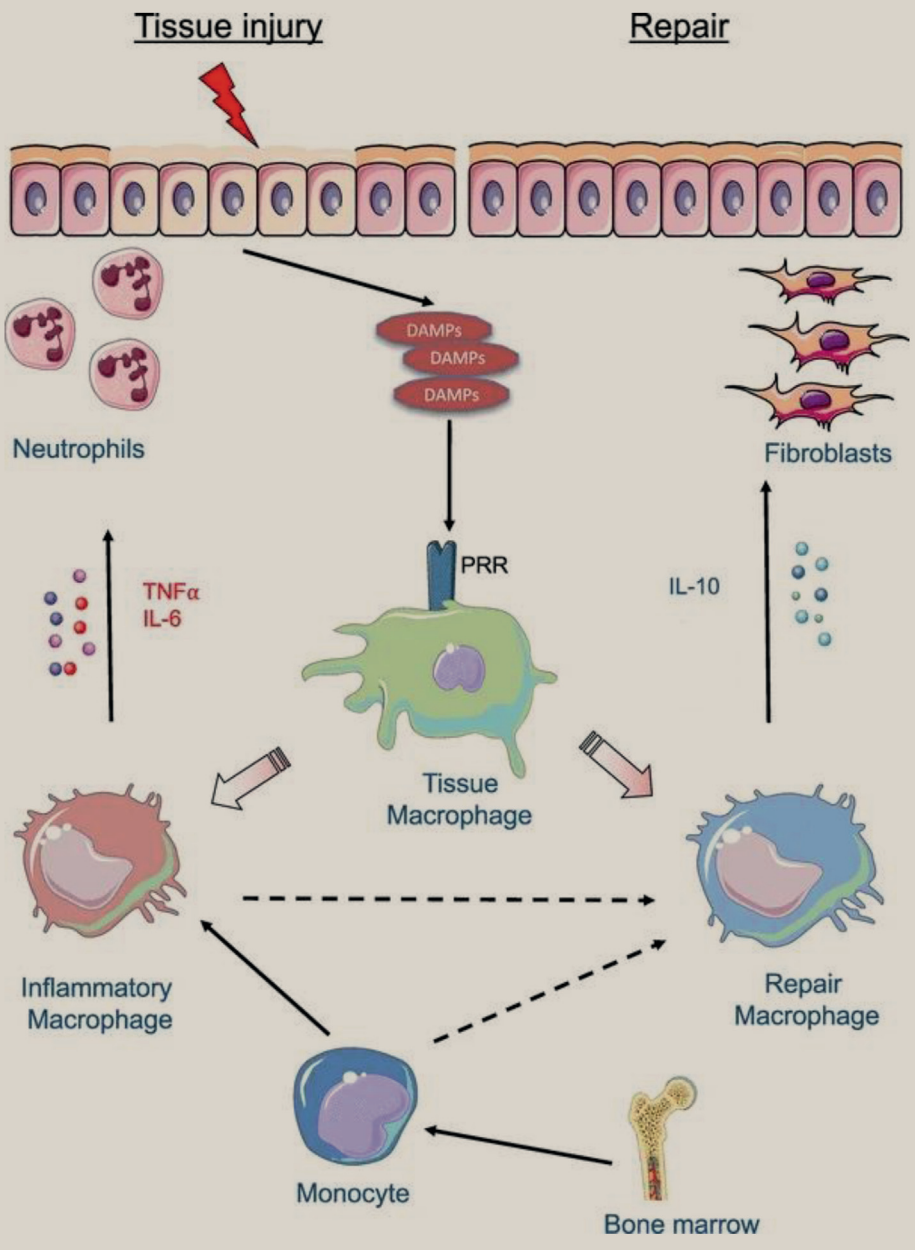
concern that due to less widespread tissue injury in penetrating trauma, the anticoagulation pathways are not activated, and therefore the risk of thrombosis may be higher.[14] In blunt trauma, the hypercoagulable state is thought to take 48 hours to occur, but venous thromboprophylaxis is an important consideration by the clinician as a result.[14]

Low fibrinogen may occur preventing the formation of a stable clot. Tranexamic acid is used to great effect now within the first

A diagram of the inflammatory response to trauma involving the pro-inflammatory cytokines interleukin-6 (Il-6) and tumour necrosis factor- α (TNF-α), and the anti-inflammatory cytokine interleukin-10 (Il-10)



DAMPs – Danger associated molecular patterns. PRR – pattern recognition receptor. PEISELER, M. & KUBES, P. 2018. Macrophages play an essential role in trauma-induced sterile inflammation and tissue repair. *European journal of trauma and emergency surgery: official publication of the European Trauma Society,* 44, 335-349.

Figure 4

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three hours of a trauma to limit fibrinolysis in a bleeding patient.[15] There are ongoing studies that look at altering the levels of fibrinogen, although the recent CRYOSTAT-2 study showed no overall improvement in 28-day mortality when high dose cryoprecipitate (equivalent to 6 g of fibrinogen) was administered to major haemorrhage patients.[16] Altering the levels of coagulation proteins is likely to require further investigation as the pathways in blunt and penetrating trauma are understood more.

Infection and immune response

Aller et al. have named a whole phase of the metabolic response to trauma on the immune response, denoting its importance.[3] During this phase there is increased activation of neutrophils, monocytes, macrophages, natural killer cells, T cells and B cells (Figure 4). This activation of the immune system all contributes to the hypermetabolic state seen. The immune cells also resulted in the increased expression of cytokines and the acute phase protein secretion by the liver (resulting in the production of CRP).[3,17] Some cytokines have a limited half-life, such as TNF-α, and their role is to induce the secretion of other cytokines, such as pro-inflammatory IL-6 and anti-inflammatory IL-10.[17] If this cytokine response is left unchecked by the body the response may be overwhelming. Pro-inflammatory cytokines, such as TNF-α and IL-6, must be downregulated by anti-inflammatory cytokines such as IL-10. Interestingly, a high level of IL-6 has been shown to be correlated with the magnitude of the trauma and the risk of complications.[17]

On a more local level, at the site of tissue injury a local inflammatory response occurs. At this site, proteins such as kinins and histamines are released.[17] Necrotic cells will release high mobility group box 1 protein, that further attracts neutrophils and macrophages to the site of injury, worsening the vascular leaking that is known to occur.[17] The complement cascade will also be activated, alongside the coagulation system described above, in an inter-connected manner.[17] These will all contribute to the attraction of the cytokines and immune cells described above.

Patients are therefore deemed at higher risk of infection following a significant trauma.[18] It has long been considered therefore as whether prophylactic antibiotics are required in trauma patients. Whilst certain patient groups are likely to benefit, such as those with an open fracture, their liberal use is not recommended and we must continue to individualize our patient care.[18]

Summary

The metabolic response to trauma is highly complex considering the variety of underlying injury causes as well as the underlying patient differences. Most is known about the short-term impact of the metabolic response to trauma and greater understanding of longer-term complications is likely required. With the growing elderly population experiencing trauma, it may also be that metabolic responses need re-evaluating as our knowledge continues to grow. ◆

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Practice points

- Trauma encompasses a wide range of pathologies and can include both blunt and penetrating mechanisms
- Initiating carbohydrate-based enteral calorie replacement within 24 hours post trauma is crucial in improving recovery by reducing muscle breakdown
- Care must be taken with aggressive fluid management following trauma as the increased vessel permeability heightens vulnerability to fluid overload and iatrogenic acute respiratory distress syndrome
- Care must be taken to manage the development of either (or both) of trauma-induced coagulopathy and hypercoagulation following a significant traumatic injury

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